

## A FEASIBILITY STUDY FOR IMAGING TISSUE ELECTROPORATION WITH ELECTRICAL IMPEDANCE TOMOGRAPHY

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### INTRODUCTION

In tissue electroporation, electrodes are inserted around the targeted tissue and electrical pulses are applied to permeabilize the cell membrane to macromolecules such as gene constructs in genetic engineering or cancer treatment drugs [1, 2]. For a specific set of voltage parameters (e.g. pulse number, frequency, duration), the effect that the electric field has depends on the voltage gradients that develop across the individual cell [2].

Currently, there is no information during the application of the pulses regarding the extent and degree of electroporation. Therefore, only the long-term consequences of the treatment can be determined, such as the cure or lack of cure of the cancer patient or the expression or the lack of expression of a gene. In this paper we demonstrate through experimental data and numerical models that electrical impedance tomography (EIT) can produce an image of the electroporated area.

### EXPERIMENTAL METHOD

Biological tissues contain extracellular and intracellular electrolytes that are good conductors of electricity. During electroporation the cell membranes, which are electrically insulating, become permeable to chemical species including electrolytes. Our hypothesis is that if the cell membrane becomes increasingly permeable to ions during electroporation, the electrical impedance of a cell should change measurably.

To quantify the impedance change of tissue during electroporation, we conducted experiments on excised rat liver slices approximately 2.5x2.0x0.25cm in size. For each experiment, a slice was placed onto a glass microscope slide surrounded by electrodes. The configuration consists of two separate sets of electrodes: one to administer the electroporation pulses and the other for detection. Experiments were conducted within 90 minutes from the time of death of the animal with the tissue stored in 0.9% NaCl at room temperature. The electroporation system is designed to supply eight 10ms squarewave pulses up to 500V/cm across the width of the tissue. This

study provides data on the electrical impedance of liver before, during and after electroporation.

### MATHEMATICAL ANALYSIS

The change in impedance during tissue electroporation may be detectable using a bioimpedance technique. EIT is an imaging method that maps the electrical impedance distribution inside the tissue. To demonstrate the ability of EIT to image electroporation we developed two computer simulations. The first was of the electroporation procedure and the second of an EIT image of this procedure.

The first simulation determines the electroporated area using an iterative technique with boundary conditions based on standard electrochemotherapy parameters. The electroporation model is a two-dimensional isotropic cross-section of a liver 7cm in diameter containing a small internal section undergoing treatment. There are two electrodes placed 10mm from one another, centered in the liver, with one electrode at 1300V and the other grounded. The surface of the tissue is assumed to be electrically isolated with a zero flux boundary condition. The data from this electroporation model is then used to generate a conductivity map for input into the EIT simulation, which then reconstructs an image of the electroporated region.

Because of its excellent convergence properties, we have chosen a modified Newton-Raphson (NR) method for the reconstruction algorithm [3]. This NR method attempts to iteratively minimize a cost function representing the overall voltage measurement differences between the simulated phantom and the reconstruction algorithm's internal model. The Jacobian needed for the NR method was calculated using a sensitivity matrix approach [4]. Marquardt regularization was used to overcome the ill-conditioning of the Jacobian matrix [5]. For our simulated phantom, 32 electrodes are equally spaced around the model periphery. To determine the effects of noise on image quality, Gaussian noise was added to each electrode measurement. No quantitative studies were performed, but a decrease in image quality began as noise levels approached 1.0% of the maximum measured voltage amplitude.

The reconstruction algorithm model consisted of a finite element mesh with an inner imaging region of 260 triangular elements, and a constrained outer ring of 464 elements. Improved resolutions can be obtained by increasing the number of electrodes and number of imaging elements but at a computational cost. The algorithm convergence criteria were typically met after approximately 15 iterations. The computations were preformed using MATLAB's partial differential equation toolbox (The MathWorks Inc.) using a Dell Precision 420 PC with an Intel 800 MHz processor.

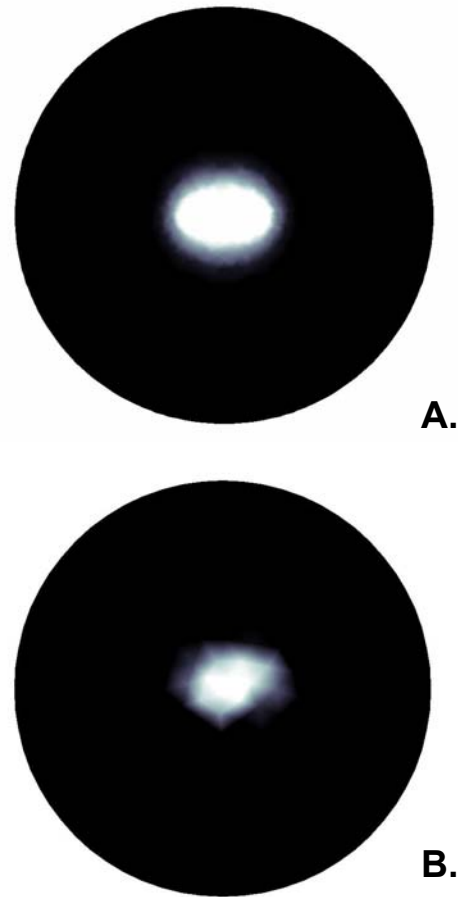
## RESULTS

Figure 1a depicts the conductivity map from the electroporation model. For elements above the threshold gradients, the conductivity is increased to the values for permeated tissue. This distribution is then passed to the EIT imaging module, and Figure1b shows the generated image using the reconstruction algorithm.

## CONCLUSION

The results in Figure 1 demonstrate that EIT can produce an image of the area affected by electroporation. It should be noted that these results are theoretical and much work remains before this method becomes a clinical technique. These results must be reproduced and verified using an actual EIT system to image physical phantoms, *ex vivo* tissue samples, and eventually *in vivo* tissues. Complexities that have been ignored in this preliminary study may need to be addressed at that stage. These include inhomogeneities in real world liver samples from larger blood vessels, non-planar currents in 3D regions, and nonlinear electrode behavior.

In molecular medicine there is no method to determine that the targeted area has been treated. This study demonstrates that monitoring of molecular medicine may potentially be achieved through the synthesis of two fairly well understood techniques, electroporation and EIT.



**Figure 1. A) Conductivity map. The white area indicates electroporated tissue. B) Generated image.**

## REFERENCES

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